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PATENT
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IN THE UNITED STATE PATENT AND TRADEMARK OFFICE

In re Application of:	)
Tadashi Mukai et al.	)
Serial No.: 09/555,026	) Group Art Unit:1614
Filed: January 18, 2002	) Examiner: Donna A. Jagoe
For: CILOSTAZOL PREPARATION	)

Assistant Commissioner for Patents
Washington, DC 20231
Sir:

RULE 132 DECLARATION

I, Tadashi Mukai do hereby declare that I am one of the inventors of the above-identified application and that I am a citizen of Japan, residing at 88, Aza-Isozaki, Kurosaki, Muya-cho, Naruto-shi, Tokushima 772-0001, Japan. That I have been employed by the OTSUKA PHARMACEUTICAL CO., LTD., a Japanese Corporation and the assignee of record of the above-identified application, since 1983. That I graduated in chemical engineering at the University of Tokushima in 1983. That recently I have been engaged in research activities relating to the development of pharmaceuticals as a manager at a pharmaceutical laboratory.

I am familiar with the history of prosecution of this application and specifically the Examiner's opinion that Claims 1 to 14 are anticipated under 35 U.S.C § 102(a) by U.S. Patent No.6,294,192 B1 and that Claims 20 to 26 are unpatentable over WO 97/48382 A2 in view of U.S. Patent No.6,294,192 B1.

To show that the claimed invention is neither anticipated by nor unpatentable

over the references, I conducted experiments as set forth below.

EXPERIMENTS

Experiment materials

(1) Bulk cilostazol powder

Four kinds of cilostazol powder having each average particle diameter of 2.0 μm, 2.5 μm, 3.4 μm and 5.4 μm were prepared by using a jet mill. In addition, a cilostazol powder having an average particle diameter of 22.20 μm was prepared by using a hammer mill.

(2) Dispersing and/or solubilizing agent

Surfactant: Sodium lauryl sulfate (trade name "SLS", Lot No.9727, manufactured by Nikko Chemicals Co., Ltd.)

(3) Other components

① Corn starch(trade name "Nisshoku Corn starch", Lot No.12.09.23.B, manufactured by Nihon Shokuhin Kako, Co., Ltd.)

② Microcrystalline cellulose(trade name "Avicel PH-301", Lot No.3155, manufactured by Asahi Kasei Corporation)

③ Hydroxypropylcellulose (trade name "HPL-C" fine powder, Lot No.II-0021, manufactured by Nippon Soda Co., Ltd.)

④ Sodium carboxymethyl starch (trade name "Pimojel", Lot No.001375591, manufactured by Matsutani Chemical Industry Co., Ltd.)

⑤ Magnesium oxide (trade name" Magnesium Oxide" light, Lot No.239, manufactured by Kyowa Chemical Industry Co., Ltd.)

⑥ Magnesium stearate (trade name "Magnesium stearate" from plant, Lot No.01042702, manufactured by Taihei Chemical Industrial Co., Ltd.)

Experiments

No.1: 700g of cilostazol powder having an average particle diameter of 2.0 μm is mixed with 7 g of sodium lauryl sulfate, 309 g of corn starch, 180 g of microcrystalline cellulose, 168 g of sodium carboxymethyl starch, 20 g of hydroxypropylcellulose, 2 g of magnesium oxide and 1020 g of water. The mixture was granulated with kneading and sieved to form granules by using a granulator (Vertical Granulator FM-VG-10, manufactured by Powrex) and a speed mill (Dalton, with a punch having a diameter of 4 mm). The resulted wet granules were dried by using a fluid-bed dryer (Multiplex, MP-01, manufactured by Powrex) and then sieved through No. 18 screen (opening 850 μm). To the sieved granules 14 g of magnesium stearate as a lublicant was added and mixed by using a drum mixer (9L) under 18 rpm for 10 minutes. The mixed granules are compressed by using a punch having a diameter of 7 mm under 812HUK (Kikusui Seisakusho Ltd.) to continuously obtain tablets containing cilostazol in the amount of 70 mg per unit.

No.2: In the same manner as in Experiment 1, tablets containing cilostazol were prepared by using the bulk cilostazol powder having an average particle diameter of 2.5 μm.

No.3: In the same manner as in Experiment 1, tablets containing cilostazol were prepared by using the bulk cilostazol powder having an average particle diameter of 3.4 μm.

No.4: In the same manner as in Experiment 1, tablets containing cilostazol were prepared by using the bulk cilostazol powder having an average particle diameter of 5.4 μm.

No.5: In the same manner as in Experiment 1, tablets containing cilostazol were prepared by using the bulk cilostazol powder having an average particle

diameter of 22.20 μm.

Cilostazol dissolution test

With respect to the tablet obtained in Experiment No.1 to 5 (containing cilostazol in the amount of 70 mg/unit), the test was carried out at 50 rpm by a Paddle Method using 900mL of an aqueous 0.3% sodium lauryl sulfate solution as a test solution. The dissolution rate after 30 minutes from the beginning of the test is shown in Table 1.

Table 1

Experiment No.	Average particle Diameter of bulk CLZ (μm)	Dissolution Rate (%)
1	2.0	92.6
2	2.5	94.4
3	3.4	90.5
4	5.4	90.5
5	22.2	78.9

Conclusion

From the results shown in Table 1, it is concluded that the tablets prepared by using bulks of cilostazol(CLZ) having an average particle diameter of 2.0 μm, 2.5 μm, 3.4 μm and 5.4 μm exhibit much higher dissolution rate than that of the tablet prepared by using the bulk of cilostazol having an average particle diameter of 22.20 μm.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: April 9, 2003 By: Tadashi Mukai

Tadashi Mukai